

Long-term management of gastroesophageal reflux disease with pantoprazole

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Abstract: Gastroesophageal reflux disease (GERD) is a chronic, relapsing disease that can progress to major complications. Affected patients have poorer health-related quality of life than the general population. As GERD requires continued therapy to prevent relapse and complications, most patients with erosive esophagitis require long-term acid suppressive treatment. Thus GERD results in a significant cost burden and poor health-related quality of life. The effective treatment of GERD provides symptom resolution and high rates of remission in erosive esophagitis, lowers the incidence of GERD complications, improves health-related quality of life, and reduces the cost of this disease. Proton pump inhibitors are accepted as the most effective initial and maintenance treatment for GERD. Oral pantoprazole is a safe, well tolerated and effective initial and maintenance treatment for patients with nonerosive GERD or erosive esophagitis. Oral pantoprazole has greater efficacy than histamine H₂-receptor antagonists and generally similar efficacy to other proton pump inhibitors for the initial and maintenance treatment of GERD. In addition, oral pantoprazole has been shown to improve the quality of life of patients with GERD and is associated with high levels of patient satisfaction with therapy. GERD appears to be more common and more severe in the elderly, and pantoprazole has shown to be an effective treatment for this at-risk population.

Keywords: pantoprazole, proton pump inhibitor, erosive esophagitis, gastroesophageal reflux disease, tolerability, efficacy

Introduction

Gastroesophageal reflux disease (GERD) is a chronic, relapsing disease that infrequently progresses (Sontag et al 2006) but is associated with a range of potentially serious esophageal complications (esophageal ulcer, esophageal stricture or obstruction, Barrett's esophagus or esophageal cancer) and extra-esophageal diseases such as respiratory problems, chest pain, angina, and increased mortality (Ruigomez et al 2004). It is characterized by reflux of the stomach contents into the esophagus, oropharynx, larynx, or airway and is associated with heartburn, acid regurgitation, and dyspepsia (Dent et al 1999; Farup et al 2001a; Shaker et al 2003; Orlando 2006). Other less common symptoms of GERD include cough, intermittent wheezing, vocal cord inflammation, atypical chest pain, dysphagia, and hoarseness. Simply put, GERD has been defined as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" (Vakil et al 2006).

Gastroesophageal reflux disease is one of the most common chronic gastrointestinal disorders (Haag and Holtmann 2003). It has been reported that GERD affects an estimated 19 million individuals in the US (Sandler et al 2002), and it can affect up to one-third of adults (Haag and Holtmann 2003). These figures are likely to underestimate the true prevalence of GERD, since many patients self-medicate and do not seek medical advice or diagnosis (Fendrick 2001). Similarly, many patients are

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not aware that they have GERD (Hollenz et al 2002). Failure to seek professional medical treatment can lead physicians to under-diagnose and under-treat GERD, with consequent poor control of symptoms, lost productivity, reduced quality of life, and an increased incidence of complications in affected patients. Ultimately, this under-diagnosis and under-treatment result in increased long-term healthcare utilization and costs.

This article provides an overview of GERD and the issues that must be considered during the long-term management of the disease; literature concerning the long-term treatment of GERD with the proton pump inhibitor (PPI) pantoprazole is then reviewed.

Long-term management issues in GERD

In healthy individuals, reflux of gastric contents occurs naturally without causing esophageal damage. However, in susceptible individuals, esophageal exposure to gastric contents causes either microscopic or macroscopic mucosal defects and the symptom of heartburn (Orlando 2006). The exact pathologic process by which this occurs is complex and yet to be fully characterized, but there are two requirements for heartburn, regardless of a diagnosis of erosive or nonerosive disease: these are high concentrations of acid within the esophageal lumen (reflux) and a damaged esophageal epithelium. When these situations co-exist, luminal acid enters the tissue where stimulation of nociceptors results in the symptom of heartburn (Orlando 2006). The major determinants of the severity of esophageal damage are the degree and duration of esophageal acid exposure in patients with impaired esophageal defenses (including increased frequency and duration of transient relaxations of the lower esophageal sphincter, impaired motility, decreased mucosal resistance, delayed gastric emptying, and presence of hiatus hernia) (Rai and Orlando 1998; Van Herwaarden et al 2000). In patients with nonerosive GERD, mucosal breaks are only apparent microscopically and are characterized by the presence of dilated intercellular spaces, whereas in patients with erosive esophagitis, breaks in the esophageal epithelium are visible on endoscopy. Nonerosive GERD can progress to erosive disease in susceptible patients (Orlando 2006) although initial severity of GERD is maintained in most patients (Vakil et al 2006). Erosive esophagitis is a chronic, recurring disease that can lead to further complications such as ulceration if long-term management is ineffective; secondary fibrosis and scarring can infrequently lead to

esophageal stricture (Orlando 1999; Sontag et al 2006; Vakil et al 2006). A 20-year follow-up of 2306 patients who received symptom-driven antireflux treatment indicated that only one patient with a normal baseline mucosa developed esophageal stricture requiring dilation (0.08%), but that 18 patients with an erosive baseline mucosa were affected (1.9%). The overall incidence of stricture in patients with GERD was <1/1,000 per year (Sontag et al 2006).

With time, patients with GERD may develop histopathological changes such as Barrett's esophagus (Spechler and Goyal 1986). GERD and Barrett's esophagus are significant risk factors for esophageal adenocarcinoma (Lassen et al 2006; Vakil et al 2006), the incidence of which has increased in Western industrialized nations over the last two decades (Bollschweiler et al 2001). In 2002, the incidence of esophageal adenocarcinoma was 26 per 100 000 person-years among patients with previously diagnosed erosive esophagitis (versus 2.79 per 100 000 person-years in the general population) in a Danish community (Lassen et al 2006). The risk of this life-threatening cancer is greatest in patients with more severe, frequent, and prolonged symptoms of GERD (Lagergren et al 1999). Severe GERD (GERD characterized by erosions, ulcers, and strictures) occurs more frequently in men, the elderly, and those of white ethnicity than in other populations (El-Serag and Sonnenberg 1997). Infection with *Helicobacter pylori* does not appear to contribute to the development of GERD (Csendes et al 1997; Labenz and Malfertheiner 1997; Raghunath et al 2003; Sharma and Vakil 2003).

Diagnosis

The differential diagnosis of GERD is often difficult. The intensity and frequency of heartburn and other symptoms of GERD are poor predictors of the presence or severity of esophageal manifestations (Johansson et al 1986; Green 1993; Fennerty et al 2002) meaning that symptom assessment alone is not a reliable method to assess the presence or severity of erosive disease (Dent et al 1999; Johnson and Fennerty 2004). However, since objective testing is not common in primary practice, it has been suggested that GERD is likely when heartburn occurs on two or more days a week, although less frequent symptoms do not preclude disease (Dent et al 1999).

Initiation of empiric therapy with acid suppressive therapy, usually a PPI, in patients with symptoms consistent with GERD is an efficient and acceptable method to confirm GERD; this method lacks specificity (Numans et al 2004).

If symptoms are relieved by therapy, a diagnosis of GERD can be assumed (DeVault and Castell 1999; Fass et al 1999, 2000; Habermann et al 2002). GERD can also be diagnosed using 24-hour pH monitoring, but this test has limitations because there is no direct information as to the extent of esophageal damage (Arango et al 2000). Additional confirmatory diagnostic tests include endoscopy, biopsy, barium radiography, examination of the throat and larynx, esophageal motility testing, emptying studies of the stomach, and esophageal acid perfusion. Of these tests, endoscopy is the only reliable method to diagnose erosive esophagitis and determine its severity (Tefera et al 1997).

Aims of treatment

The main aim of GERD treatment should be rapid and sustained achievement of comprehensive symptom resolution, because this is associated with marked improvement—often normalization—in health-related quality of life (Revicki et al 1999). The other primary aims are to heal esophageal mucosal damage if it is present and to prevent relapse of erosive esophagitis in the hope that this will reduce the development of other serious complications.

Adequate treatment of GERD should either prevent repeated reflux of gastric contents into the esophagus or reduce the damaging effect of gastric acid. As no pharmaceutical agent can fully correct the motor dysfunction responsible for acid reflux into the esophagus, acid suppression remains the most effective way to relieve symptoms and to promote healing of esophagitis in patients with GERD (Orlando 1997).

Treatment options

A number of pharmacological and surgical treatment options are available for patients with GERD. For most patients, initial acid suppressive therapy with a PPI is recommended. Once healing is achieved, the majority of patients with erosive esophagitis will require continued long-term (maintenance) acid suppressive treatment, usually with a lower dosage of their initial acid-suppressive therapy. This is because GERD is a chronic, usually lifelong disease that often relapses once treatment is stopped. In fact, relapse rates of 81% to 90% have been reported in patients with healed erosive esophagitis 6 to 12 months after drug therapy was withdrawn (Hetzel et al 1988; Chiba 1997; Carlsson et al 1998) and it is generally accepted that symptoms will persist in most patients (Vakil et al 2006).

Pharmacological options

The main acid suppressive agents available for patients with GERD are antacids, H₂-receptor antagonists, and PPIs. Antacids do not usually provide sufficient acid suppression for patients with GERD. H₂-receptor antagonists decrease gastric acid secretion by competitive and reversible blockade of histamine H₂-receptors on the parietal cells of the gastric mucosa. H₂-receptor antagonists are significantly more effective than antacids for suppressing acid secretion, but have a slower onset of action (Netzer et al 1998; Wyeth et al 1998). Use of H₂-receptor antagonist is limited by drug tolerance, which can result in about a 50% reduction in efficacy that cannot be reversed by dose increases (Nwokolo et al 1990; Kahrilas et al 1999). Over-the-counter preparations of low-dose H₂-receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine) are also available. These are relatively safe, but are not effective in the vast majority of patients (Shaw et al 2001).

Proton pump inhibitors are widely recognized as the most effective agents for treating GERD. They are the mainstay of initial GERD management (DeVault and Castell 1999) and are the preferred agents for maintenance therapy in patients with healed erosive esophagitis (DeVault and Castell 1999; Crawley and Maclin Schmitt 2000). PPIs provide more rapid symptom control and better healing of erosive esophagitis than both H₂-receptor antagonists and antacids (Chiba et al 1997; Dent et al 1999; DeVault and Castell 1999; Caro et al 2001; Donnellan et al 2004).

Proton pump inhibitors block the final step in the secretion of hydrochloric acid by binding to and inactivating H⁺/K⁺ATPase in parietal cells of the gastric mucosa (Bell and Hunt 1992; Sachs 1997). PPIs thus produce a considerable but dose-dependent elevation of gastric pH (Dajani 2000). The prolonged hypochlorhydria seen with PPI therapy has raised safety concerns for patients receiving long-term therapy with these agents (possible enterochromaffin-like cell hyperplasia and gastric carcinoids, colorectal adenocarcinoma and polyps, and bacterial overgrowth as a result of achlorhydria). However, the magnitude of hypergastrinemia associated with PPI use is similar to that observed after vagotomy, and is 3- to 6-fold lower than that observed with pernicious anemia. Evidence to date indicates that any morphological changes in gastric endocrine cells are minimal, self-limiting, nondysplastic and non-neoplastic, suggesting that hypergastrinemia observed during PPI therapy has little clinical significance (Freston 1997). Thus, monitoring of serum gastrin levels and fundic enterochromaffin-like cells

is of no clinical relevance even during long-term therapy with PPIs (Arnold 1994). PPIs are associated with a low rate of drug-drug reactions, other than those expected by the lowering of intragastric pH (Labenz et al 2003; Robinson and Horn 2003). Of the PPIs, omeprazole has the highest risk for hepatic-based interactions, and rabeprazole and pantoprazole appear to have the lowest risk (Robinson and Horn 2003). Of these lower risk agents, pantoprazole is the only PPI with a well characterized interaction profile (Blume et al 2006).

Surgery

Although surgery (open, endoscopic, or laparoscopic) is an option for some patients with GERD, the outcomes of corrective procedures vary widely depending on the experience and skill of the surgeon (Watson et al 1996; Johnson 2003). Surgery is not an ideal option for the majority of patients, and many patients will continue to use acid reducing medications on a regular basis after undergoing surgery (Spechler et al 2001; Johnson 2003). In comparison with pharmacotherapy in the US, surgical antireflux therapy (open Nissen fundoplication) produces no significant differences in grade of esophagitis, frequency of treatment of esophageal stricture, and subsequent antireflux operations, incidence of esophageal cancer, quality of life measures, and overall satisfaction with antireflux therapy when assessed more than 9 years after initiation of therapy (Spechler et al 2001). Similarly, in Europe, PPI therapy demonstrates similar efficacy to open antireflux surgery in terms of prevalence of Barrett's esophagus or strictures requiring dilatation, incidence of GERD-associated symptoms or quality of life at 3 years' follow up (Lundell et al 2000), but after 5 years is associated with lower total medical costs (operation, endoscopy, visits to the outpatient clinic, and medication) for chronic GERD (Myrvold et al 2001). Laparoscopic fundoplication is not without complications: surgical complications such as gastric perforation or hernia can occur; medical therapy is required for control of heartburn in approximately one third of patients after this procedure; and new gastric symptoms are common after surgery (Vakil et al 2003).

Efficacy, safety, and tolerability of pantoprazole

Efficacy

Initial therapy

Oral pantoprazole is an effective treatment option for the initial treatment of nonerosive GERD or erosive esophagitis. It is most effective for healing erosive esophagitis when

administered at a dose of 40 mg once daily (van Rensburg et al 1996; Richter and Bochenek 2000).

In patients with endoscopically confirmed mild to severe erosive esophagitis, oral pantoprazole 20 mg/day or 40 mg/day is more effective for healing of erosions and relief of GERD symptoms than the H₂-receptor antagonists with which it has been compared (Cheer et al 2003; Bochenek et al 2004) and generally has similar efficacy to other PPIs on a mg per mg basis (Cheer et al 2003; Scholten et al 2003; Gillissen et al 2004; Achim et al 2005; Glatzel et al 2006). Oral pantoprazole 20 mg daily also provided clinical improvement in symptoms of erosive esophagitis in children aged 6 to 13 years enrolled in a small uncontrolled trial (Madrazo-de la Garza et al 2003). These latter findings are supported by the results of two recently completed studies. In these studies, oral pantoprazole at doses of 20 mg and 40 mg once daily for 8 weeks rapidly reduced symptom scores in 53 children aged 5 to 11 years with erosive or histological esophagitis ($p < 0.001$) (Tolia et al 2006) and in 136 adolescents aged 12 to 16 years with clinically diagnosed GERD ($p < 0.001$) (Tsou et al 2006). Pantoprazole 10 mg daily also produced significant improvement in symptoms, but was not as effective as the higher doses in children (Tolia et al 2006).

Maintenance therapy

Pantoprazole 20 mg or 40 mg daily as maintenance therapy prevents relapse of erosive esophagitis for 6 to 24 months in most patients with healed disease (Mossner et al 1997; Escourrou et al 1999; Van Rensburg et al 1999; Plein et al 2000), regardless of patients' initial disease severity (Metz and Bochenek 2003; Richter et al 2004). Pantoprazole 20 mg once daily has generally shown similar efficacy for preventing endoscopic or symptomatic relapse to pantoprazole 40 mg once daily (Escourrou et al 1999; Plein et al 2000). In the larger of the two trials designed to statistically compare these pantoprazole regimens, daily doses of 20 mg and 40 mg maintained 75% and 78% of patients, respectively, in endoscopic remission after 12 months, with Savary-Miller stage I disease accounting for about 50% of the endoscopic relapses (Plein et al 2000). Symptomatic remission rates after 12 months were also similar with each pantoprazole regimen: 77% with the 20 mg dose and 76% with the 40 mg dose. No correlation was seen between endoscopic relapse and perception of symptoms, or between the baseline severity of GERD and the maintenance dose of pantoprazole (Plein et al 2000). However, in two dose-ranging comparisons with ranitidine, patients receiving pantoprazole 40 mg daily were

significantly more likely to remain in remission than patients receiving pantoprazole 20 mg daily ($p < 0.03$ and $p < 0.001$) (Table 1) (Metz and Bochenek 2003; Richter et al 2004).

In comparisons with other active treatments, pantoprazole has demonstrated high remission rates. Pantoprazole 20 mg or 40 mg is more effective than ranitidine 150 mg once or twice daily for maintaining healing of GERD after 12 months of therapy (Table 1) (Adamek et al 2001; Metz and Bochenek 2003; Richter et al 2004). Patients receiving pantoprazole have significantly higher endoscopic remission rates at 12 months (Table 1) and symptomatic control is also significantly better, as measured by the proportion of symptom-free patients at 12 months (Table 1) (Adamek et al 2001), the number of symptom-free days during the 12-month period (83% of days vs 58% of days, $p < 0.001$ [Richter et al 2004] and 78% vs 48%, $p < 0.001$ [Metz and Bochenek 2003]) and the number of nights without heartburn (93% of nights vs 77% of nights, $p = 0.001$ [Richter et al 2004]

and, $p = 0.002$ [Metz and Bochenek 2003]). In addition, pantoprazole maintains patients in remission for a longer period of time than does ranitidine (Metz and Bochenek 2003). Pantoprazole is more effective than ranitidine in maintaining endoscopically confirmed healing, regardless of initial disease severity or *H. pylori* status (Metz and Bochenek 2003, Richter et al 2004).

Only a few studies have evaluated the efficacy of maintenance therapy with pantoprazole in comparison with other PPIs. The data available indicate that pantoprazole 20 mg has similar efficacy to omeprazole 20 mg for maintaining endoscopic and symptomatic remission in patients with healed erosive esophagitis (Lauritsen et al 2000). In comparisons with esomeprazole 20 mg daily, there are two studies showing conflicting results. Whereas the study by Labenz and colleagues (2005) showed esomeprazole 20 mg daily to be superior to pantoprazole 20 mg daily, the study by Goh and colleagues (2007) showed esomeprazole 20 mg

Table 1 Randomized clinical trials comparing the efficacy of maintenance therapy with pantoprazole versus other acid suppressing agents in patients with healed erosive esophagitis^a

Reference	Treatment (No of patients)	Endoscopic remission rate at study end (% patients)	Symptomatic control at study end (% patients)
Comparisons with other proton pump inhibitors			
Goh et al 2007 (double-blind, 6-month trial)	Pantoprazole 20 mg once daily (636)	84 ^b	
	Esomeprazole 20 mg once daily (667)	85 ^b	
Labenz et al 2005 (double-blind, 6-month trial)	Pantoprazole 20 mg once daily (1389)	77 ^{**}	88.5 [†]
	Esomeprazole 20 mg once daily (1377)	88	92
Lauritsen et al 2000 (double-blind, 12-month trial)	Pantoprazole 20 mg once daily (211)	77	83
	Pantoprazole 40 mg once daily (218)	83	87
	Omeprazole 20 mg once daily (210)	81	86
Comparisons with ranitidine			
Adamek et al 2001 (double-blind, 12-month trial)	Pantoprazole 20 mg once daily (199)	66 ^{**}	73% [†]
	Ranitidine 150 mg once daily (104)	34	65%
Metz et al 2003 (double-blind, 12-month trial)	Pantoprazole 10 mg once daily (89)	40	
	Pantoprazole 20 mg once daily (93)	68	
	Pantoprazole 40 mg once daily (94)	82	
	Ranitidine 150 mg twice daily (95)	33 [†]	
Richter et al 2004 (double-blind, 12-month trial)	Pantoprazole 10 mg once daily (88)	46	
	Pantoprazole 20 mg once daily (88)	55 [*]	
	Pantoprazole 40 mg once daily (85)	78 [*]	
	Ranitidine 150 mg twice daily (88)	21	

Note: ^aResults of intention-to-treat analyses; ^bEndoscopic plus symptomatic control; ^{*} $p < 0.001$; ^{**} $p \leq 0.0001$ versus esomeprazole or ranitidine; [†] $p < 0.001$ versus all doses of pantoprazole.

daily to be as effective as pantoprazole 20 mg daily in keeping patients in combined endoscopic and symptomatic remission (Table 1).

In the above trials the symptoms assessed were heartburn, dysphagia or pain on swallowing, and acid regurgitation. In some instances, additional gastric symptoms were also included (Plein et al 2000; Labenz et al 2005), but long-term data regarding the efficacy of pantoprazole for control of respiratory or laryngeal symptoms of GERD are not available. However, long-term high-dose PPI therapy is the first-line approach to controlling these extraesophageal GERD symptoms (Halstead 2005).

Pantoprazole has also demonstrated efficacy in difficult-to-treat patients. In 66 patients with aggressive, complicated GERD refractory to H₂-receptor antagonists, but healed with oral pantoprazole, continued therapy with oral pantoprazole 40 mg daily maintained remission in most patients at 24 months (percentages were not reported) (Bardhan et al 2001).

It is common for many patients with mild disease and infrequent symptom relapses to use a PPI only when symptoms demand. Patients with symptomatic or mild erosive GERD are therefore ideal candidates for on-demand or intermittent treatment (Bardhan 2003). On-demand treatment with oral pantoprazole 20 mg or 40 mg daily provided effective symptomatic control in 634 patients with endoscopically confirmed Savary-Miller grade 0/I GERD and heartburn, with the mean perceived average daily symptom load of heartburn over a 6-month period reduced from 3.93 with placebo to 2.71 with the 40 mg dose and 2.91 with the 20 mg dose ($p < 0.0001$ for both pantoprazole doses vs placebo) (Scholten, Dekkers, et al 2005). The discontinuation rate due to insufficient control of heartburn or unsatisfactory treatment (insufficient control of heartburn or other gastrointestinal symptoms) was significantly lower in both pantoprazole groups than in the placebo group, despite placebo recipients using significantly more antacid therapy ($p < 0.05$ for all pantoprazole vs placebo comparisons). No significant differences between pantoprazole 20 mg and 40 mg were reported.

These advantages of on-demand pantoprazole over placebo for control of heartburn were confirmed for a wider range of GERD-associated symptoms in another trial. On-demand treatment with pantoprazole 20 mg for 6 months was effective, compared with placebo, in maintaining control of the symptoms of heartburn, acid regurgitation, and pain on swallowing in 439 patients with healed Savary-Miller

grade 0/I GERD. Patients' perceived average daily symptom load was 1.5 and 2.2 for the pantoprazole and placebo group, respectively ($p < 0.05$), and pantoprazole-treated patients experienced fewer episodes requiring treatment ($p < 0.01$), and had a lower discontinuation rate due to insufficient control of symptoms or unsatisfactory treatment. Again, antacid usage was significantly higher in placebo recipients than in pantoprazole-treated patients ($p < 0.05$) (Kaspari et al 2005).

In the only identified comparison of on-demand administration of active treatments, pantoprazole 20 mg significantly reduced the symptom load for heartburn compared with esomeprazole 20 mg (1.12 vs 1.32, $p = 0.0115$) in 199 patients with Los Angeles classification grade A or B GERD or nonerosive GERD and moderate or severe heartburn. Mean intensities of heartburn were significantly lower in the pantoprazole compared with the esomeprazole treatment group during the 6 months on-demand treatment (1.10 vs 1.33, $p = 0.0096$) (Figure 1) (Scholten, Bohuschke, et al 2005).

Safety and tolerability

Results of numerous clinical trials indicate that oral pantoprazole is safe and well tolerated for short-term treatment of GERD and for longer term maintenance therapy in patients with healed erosive esophagitis. Oral pantoprazole at dosages of up to 40 mg daily was safe and well tolerated in studies of 1 to 2 years in duration (Mossner et al 1997; Escourrou et al 1999; Van Rensburg et al 1999; Plein et al 2000; Adamek et al 2001; Metz and Bochenek 2003; Richter et al 2004; Labenz et al 2005). Although serum gastrin levels tended to increase initially in some, but not all, studies, they generally stabilized and were not associated with adverse histological findings. Adverse events most commonly experienced by patients receiving pantoprazole in these long-term trials are those expected in patients receiving PPI therapy. Events most frequently include diarrhea, nausea, vomiting, headache, dizziness, abdominal pain, infection, and raised liver enzymes. These are usually of mild to moderate intensity and seldom necessitate discontinuation of treatment.

Two longer-term trials have been performed. One reported data for treatment with oral pantoprazole for up to 3 years. In this study, only 4 of 111 patients had adverse events definitely related to pantoprazole. Elevations in gastrin were modest and there were no significant changes in gastric endocrine cells (Bardhan et al 2001). The other

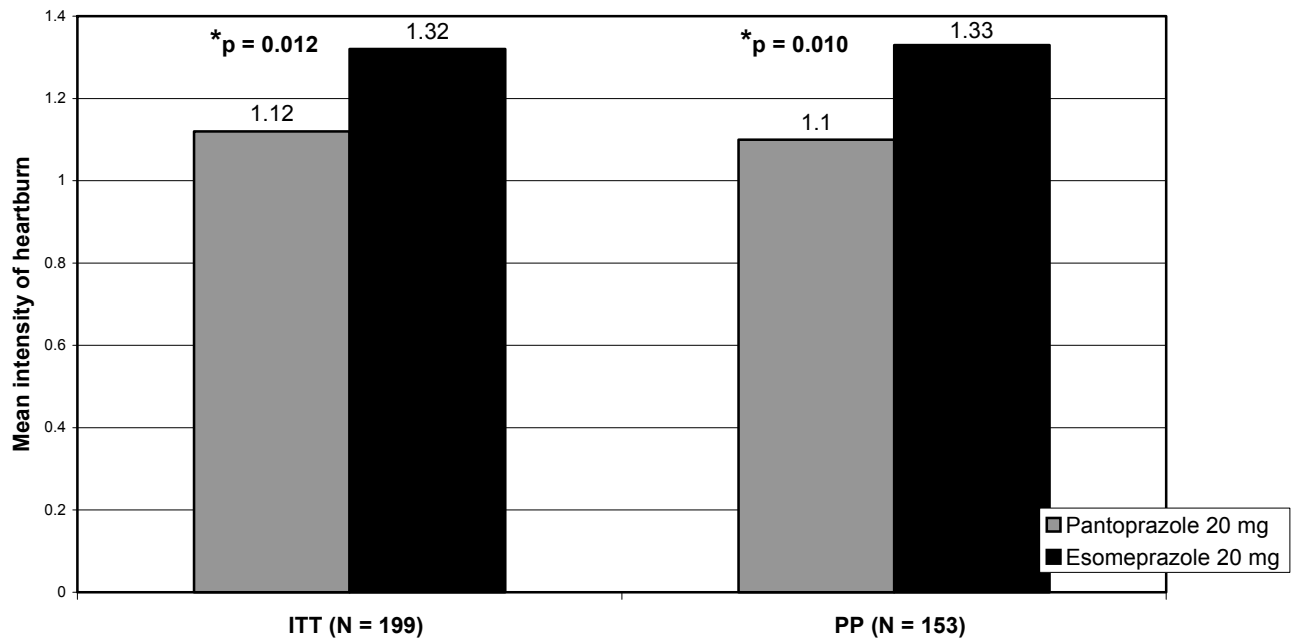


Figure 1 On-demand therapy with pantoprazole leads to lower heartburn intensity than with esomeprazole in patients with mild GERD.
Note: *Statistically significant difference; The intensity of symptoms was rated on a 4 point-scale (0: none, 1: mild, 2: moderate, 3: severe).
Abbreviations: ITT, intention to treat population; PP, per protocol population.

is an ongoing 10-year study, in which maintenance therapy with pantoprazole 40 mg to 160 mg daily was well tolerated in patients with healed peptic ulcers or erosive esophagitis. There were no increases in signs associated with an enhanced risk of gastric cancer, although fasting serum gastrin levels increased slightly after the second year of treatment but remained at this level thereafter. Of 134 patients originally enrolled in this long-term study, 99 patients were treated with pantoprazole for at least 5 years, and 25 had completed 10 years of treatment (Heinze et al 2003).

The safety profile of pantoprazole in elderly patients is discussed later in this review. Short-term (up to 8 weeks) use of pantoprazole is safe and well tolerated in children and adolescents (aged 5 to 16 years) (Madrado-de la Garza et al 2003; Tolia et al 2006; Tsou et al 2006).

Impact of GERD on quality of life

Patients with GERD have significantly ($p < 0.05$) poorer health-related quality of life than the general population (McDougall et al 1996; Revicki et al 1998; Enck et al 1999; Kaplan-Machlis et al 1999; Farup et al 2001a; Pare et al 2003), patients with diabetes or hypertension (Revicki et al 1998; Enck et al 1999), and patients with severe angina pectoris or mild heart failure (Dimenas et al 1993). Although

there are no relevant differences in health-related quality of life between patients with Barrett's esophagus, erosive esophagitis and non-erosive GERD (Kulig et al 2003), impairment is proportional to the frequency and severity of symptoms, regardless of the presence or absence of esophagitis (Dimenas et al 1996; Dent et al 1999; Kaplan-Machlis et al 1999), is more severe in females and younger patients (Holtmann et al 2006b) and is exacerbated by the presence of nocturnal symptoms (Farup et al 2001a, 2001b). Although the frequency and intensity of acid complaints significantly influence the health-related quality of life of patients with GERD (Holtmann et al 2006a), a number of other gastrointestinal symptoms, such as upper abdominal/stomach complaints, lower abdominal/digestive complaints, and nausea, also have a major role (Malagelada et al 2006). The impact of GERD is most striking on measures of pain, mental health, and social function (Revicki et al 1998; Enck et al 1999; Farup et al 2001a). The presence of GERD is also associated with reduced work productivity for affected individuals in the labor force (Henke et al 2000; Sandler et al 2002).

The treatment of GERD improves symptoms and health-related quality of life outcomes (Wiklund et al 1998; Revicki et al 1999; Prasad et al 2003). Control of heartburn strongly

predicts improvement in health-related quality of life during the acute treatment of GERD (Pare et al 2003). Although no trials of maintenance therapy have reported quality of life assessments for pantoprazole, several studies have evaluated the effect of short-term pantoprazole on health-related quality of life, and results of these studies generally showed the PPI to improve health-related quality of life (de-Souza-Cury et al 2006) and be superior to H₂-receptor antagonists (Kaspari et al 2001; Pare et al 2003). Health-related quality of life improved more rapidly and to a greater extent following treatment with pantoprazole 40 mg once daily compared with nizatidine 150 mg twice daily in a total of 208 patients with GERD characterized by heartburn (with or without erosive esophagitis). After 7 days, scores for all assessment scales improved more with pantoprazole than nizatidine. Patients receiving pantoprazole showed significantly greater improvement in two SF-36 domains, bodily pain ($p < 0.01$) and vitality ($p < 0.05$), and in the gastrointestinal system rating scale (GSRS) reflux score ($p < 0.01$). After 28 days of treatment, the changes in scores relative to baseline were still greater with pantoprazole than with nizatidine (Pare et al 2003). Similarly, in comparison with ranitidine, quality of life parameters tended to improve more with pantoprazole 20 mg once daily than ranitidine 150 mg twice daily according to the gastrointestinal quality of life index (GIQLI) and SF-36, with a significant advantage seen for pantoprazole in the SF-36 vitality score ($p < 0.05$), in a mixed population of patients with nonerosive GERD or endoscopically confirmed erosive esophagitis. Patients' assessment of treatment also appeared to be more favorable for pantoprazole in this short-term study (Kaspari et al 2001). Patient satisfaction with treatment is similar with pantoprazole, omeprazole, and lansoprazole (at 4 and 8 weeks, respectively, patient satisfaction was 79% and 91% [pantoprazole], 79% and 89% [omeprazole multiple unit pellet system (MUPS)] and 76% and 86% [lansoprazole] in one study [Mulder et al 2002]).

Recently, a new GERD specific, reliable, sensitive, and validated questionnaire for the evaluation of health-related quality of life was developed. The GERDyzer™ covers 10 dimensions of quality of life (general well-being, pain/discomfort, physical health, energy, daily activities, leisure activities, social life, diet/eating/drinking habits, mood and sleep) and has demonstrated very high internal consistency, good test-retest reliability, responsiveness and construct validity in patients treated with pantoprazole (Holtmann et al 2005). Using this questionnaire in conjunction with the ReQuest™- GI (Stanghellini V et al 2005), all dimensions

of treatment satisfaction were shown to increase during 4 weeks of treatment with pantoprazole, with good treatment satisfaction reported after the first week of therapy (DeVault et al. 2006).

Treating patients with GERD is about 2-fold more costly than treating those without GERD (Bloom et al 2001). However, PPIs have the lowest total cost per patient of the available pharmacological treatments, when total costs (defined as the costs of diagnosis and initial treatment, and the costs associated with treatment success, treatment failure and remission) are calculated, despite having higher acquisition costs than other acid suppressive agents (Holzer et al 1998). Scant pharmacoeconomic data specific for pantoprazole are available. The only study identified, a modelling study in the Netherlands, showed that pantoprazole may have a more favorable pharmacoeconomic profile than omeprazole. Assumptions were based on available documentation concerning the effectiveness and costs of omeprazole and pantoprazole and findings are only valid if the substitution of omeprazole by pantoprazole can be achieved without loss of efficacy or tolerability (van Hout et al 2003).

Special considerations in the elderly

GERD appears to be more common and more severe in the elderly than in younger individuals; in fact age is an important risk factor for the development of severe forms of GERD (El-Serag and Sonnenberg 1997; Johnson and Fennerty 2004). In the primary care setting in the US, as many as 20% of older patients report acid reflux (Mold et al 1991), and in a Japanese study, the prevalence of erosive esophagitis in patients aged >70 years was more than triple the prevalence in patients younger than 39 years (Maekawa et al 1998). In common with the general population, the intensity and frequency of heartburn and other symptoms of GERD are poor predictors of the presence or severity of esophageal manifestations. In addition, older patients are less likely to experience severe heartburn than younger patients (Johnson and Fennerty 2004) and the majority (over 75%) do not experience acid regurgitation as an initial symptom (Räihä et al 1991; Pilotto and Franceschi 2003). More frequently, elderly patients with GERD report symptoms such as dysphagia, vomiting and respiratory difficulties, anorexia, weight loss, and anemia-melena (Pilotto and Franceschi 2003). Because of this different symptom profile of GERD in the elderly, the disease, particularly in milder form, may remain undiagnosed for a considerable period of time (Maekawa et al 1998) resulting in hospital admittance for more severe disease (Zimmerman et al 1997).

Elderly patients require endoscopy as the initial diagnostic test for GERD, irrespective of the severity or duration of their symptoms—endoscopy is even indicated in elderly patients without current typical symptoms, but with a past history of GERD (Richter 2000). However, endoscopy can be associated with the risk of complications, particularly in elderly patients with heart or pulmonary disease, and so use of well validated symptom assessment tools may increasingly have a role in the diagnosis and long term management of GERD in elderly patients. Based on their safety profiles and success in the general patient population, PPIs as a class are considered first-line treatment for GERD and erosive esophagitis in the elderly (Bacak et al 2006).

Results of a retrospective analysis, based on combined data from two prospective, double-blind, randomized trials in patients with Hetzel-Dent grade ≥ 2 erosive esophagitis, show that healing rates with pantoprazole 40 mg are similar in elderly patients and in younger patients. At 8 weeks, healing rates were 86% in the 44 patients aged ≥ 65 years and 83% in the 210 patients aged < 65 years. Pantoprazole was more effective than a combined placebo/nizatidine treatment group ($p < 0.001$) (DeVault et al 2003).

Results of a prospective study have confirmed the efficacy of oral pantoprazole in 164 patients aged ≥ 65 years with Savary-Miller grade I-III GERD. Patients initially received pantoprazole 40 mg daily for 8 weeks and 81% achieved documented healing of erosive esophagitis. All healed patients subsequently received maintenance therapy with pantoprazole 20 mg daily; 82% remained in remission at 6 months. Continued therapy with pantoprazole 20 mg daily for a further 6 months maintained a remission rate of 80% at 1 year, whereas switching to placebo for the last 6 months of the trial resulted in a remission rate of 30% (Pilotto et al 2003). These results show that pantoprazole is highly effective for healing and reducing the relapse of erosive esophagitis, and that discontinuing active treatment after 6 months is associated with a significant increase in the risk of relapse. In this study, the most commonly reported adverse events were glossitis, headache, and diarrhea. These findings are in agreement with data for nonelderly populations.

When treating elderly patients with GERD, concomitant medications should be considered for two main reasons. Firstly, it is known that a number of medications commonly prescribed for elderly patients may promote gastroesophageal reflux and, secondly, drug interactions may be of particular importance in these patients as they are frequently receiving multiple drug therapies (Pilotto et al 2005; Gorard 2006;

Steinman et al 2006). When considering treatment with PPIs, it is important to note that interactions caused by changes in gastric pH are a group-specific effect, but each PPI differs in its propensity to interact with other drugs and the extent to which its interaction profile has been defined. The interaction profiles of omeprazole and pantoprazole have been studied most extensively: omeprazole carries a considerable potential for drug interactions, whereas pantoprazole appears to have lower potential for interactions with other medications. The interaction profiles of esomeprazole, lansoprazole, and rabeprazole have been less extensively investigated, but evidence suggests that lansoprazole and rabeprazole have weaker potentials for interactions than omeprazole, and esomeprazole has a propensity for drug interactions similar to that of omeprazole. (Blume et al 2006). This pharmacokinetic profile suggests that pantoprazole is well suited for use in elderly patients who as a group frequently present with comorbidities and receive multiple therapies.

Conclusion

The optimal treatment of GERD is vital for a number of reasons. GERD is a chronic, relapsing disease that can progress to major complications; affected patients have significantly poorer health-related quality of life than the general population, with impairment being proportional to the frequency and severity of symptoms; and as GERD requires continued therapy to prevent relapse and complications, most patients with erosive esophagitis require long-term acid suppressive treatment. Thus GERD results in a significant cost burden.

The effective treatment of GERD provides symptom resolution and high rates of remission in erosive esophagitis, lowers the incidence of GERD complications, improves health-related quality of life and reduces the cost of this disease. PPIs are accepted as the most effective treatment for GERD and are the mainstay of initial GERD management, providing more rapid symptom control and better healing of erosive esophagitis than H_2 -receptor antagonists and antacids. PPIs are also the preferred agents for maintenance therapy in patients with healed erosive esophagitis (Lauritsen et al 2003). As few differences in safety or efficacy have been reported between the available PPIs, the decision to select one PPI over another is most likely to be based on the agents' acquisition costs, formulations, Food and Drug Administration-labeled indications, and overall safety profiles (Welage and Berardi 2000).

The data reviewed here show that oral pantoprazole is a safe, well tolerated and effective initial and maintenance

treatment for patients with nonerosive GERD or erosive esophagitis. Oral pantoprazole has greater efficacy than that of H₂-receptor antagonists and generally has similar efficacy to other PPIs for the initial and maintenance treatment of GERD. In addition, oral pantoprazole has been shown to improve the quality of life of patients with GERD and is associated with high levels of patient satisfaction with therapy. GERD appears to be more common and more severe in the elderly. Furthermore, as elderly are taking multiple medications at the same time, or drugs with a narrow therapeutic window, drug interactions may be of particular importance in those patients. Pantoprazole has also shown to be an effective and safe treatment for this at-risk population.

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